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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,065	BRASCH ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2005* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20, 27, and 30-57* is/are pending in the application.

4a) Of the above claim(s) *40-43 and 52-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20, 27, 30-39, 44-51, 56, and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/27/05* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Response to Amendment

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE and the amendment filed on January 27, 2005 have been entered. The claims pending in this application are claims 14-20, 27, and 32-57 wherein claims 40-43 and 52-55 has been withdrawn due to species election. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendments. The following rejections are based on amendments and claims 14-20, 27, 32-39, 44-51, 56, and 57 will be examined.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(f) he did not himself invent the subject matter sought to be patented.

3. Claims 14-20, 27, 32, 33, 44-46, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Stemmer (US Patent No. 5,605,793, published by February 25, 1997).

Stemmer teaches method for *in vitro* recombination which can be used in many different genes encoded proteins.

Regarding claim 14, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein" is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches inserting one or more double-stranded oligonucleotides comprising one or more mutations into double-stranded random fragments, denaturing the resultant mixture of the double-stranded random fragments and oligonucleotides into single-stranded fragments, incubating the resultant population of single-stranded fragments with a polymerase under conditions which results in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded polynucleotide (see column 3, second paragraph). Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is capable of inserting randomly into a target nucleic acid molecule (ie., one or more

double-stranded random fragments), one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is one or more integration sequences as recited in claim 14. Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer are inserted into one or more double-stranded random fragments in the presence of a polymerase and form a mutagenized double-stranded polynucleotide, one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer contain one or more recombination sites as recited in claim 14. Therefore, Stemmer discloses inserting one or more integration sequences (ie., one or more double-stranded oligonucleotides comprising one or more mutations) comprising at least one recombination site into at least one nucleic acid molecule (ie., double-stranded random fragments) to produce one or more integration sequence-containing nucleic acid molecules as recited in claim 14. Since the mutagenized double-stranded polynucleotide taught by Stemmer is cloned into an appropriate vector (see column 8, lines 60 and 61) and it is known that a cloning process must used a ligase, according to the definition of "recombination protein" in the specification, a ligase is a recombination protein and Stemmer discloses transferring one or more integration sequence-containing nucleic acid molecules formed in the inserting step comprising at one recombination site into one or more vectors in the presence of one or more recombination proteins (ie., a ligase) as recited in claim 14.

Regarding claims 16 and 18, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid

molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches inserting one or more double-stranded oligonucleotides comprising one or more mutations into double-stranded random fragments, denaturing the resultant mixture of the double-stranded random fragments and oligonucleotides into single-stranded fragments, incubating the resultant population of single-stranded fragments with a polymerase under conditions which result in the annealing of said single-stranded fragments at regions of identity between the single-stranded fragments and formation of a mutagenized double-stranded polynucleotide (see column 3, second paragraph). Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is capable of inserting randomly into a target nucleic acid molecule (ie., one or more double-stranded random fragments), one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer is one or more integration sequences as recited in claim 16. Since one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer are inserted into one or more double-stranded random fragments in the presence of a polymerase and form a mutagenized double-stranded polynucleotide, one or more double-stranded oligonucleotides comprising one or more mutations taught by Stemmer contain one or more recombination sites as recited in claim 16. Therefore, Stemmer discloses inserting one or more integration sequences (ie., one or more double-stranded oligonucleotides comprising one or more mutations) comprising at least one recombination site into at least one nucleic acid molecule (ie., double-stranded random fragments) as recited in claim 16. Since, after

restriction digestion, the digested mutagenized double-stranded polynucleotide taught by Stemmer is cloned into an appropriate vector (see column 8, lines 60 and 61 and column 12) and it is known that a cloning process must used a ligase, according to the definition of "recombination protein" in the specification, the digested mutagenized double-stranded polynucleotide taught by Stemmer is an integration sequence-containing nucleic acid molecule comprising at least first and second recombination sites as recited in claim 16 wherein 5' and 3' ends of restriction sites of the digested mutagenized double-stranded polynucleotide are a first and a second recombination site and Stemmer discloses causing said at least first and second recombination sites to recombine in the presence of at least one recombination protein (ie., a ligase) as recited in claim 16. Since Stemmer teaches that 5' and 3' ends of restriction sites of the digested mutagenized double-stranded polynucleotide are a first and a second recombination site, Stemmer discloses that said first and second recombination sites are separated by a portion of said integration sequence-containing nucleic acid molecule as recited in claim 18.

Regarding claims 15 and 27, since double-stranded random fragments are generated from a PCR product of the wild-type LacZ alpha gene (see column 11), the double-stranded random fragments are genomic DNA as recited in claims 15 and 27.

Regarding claim 17, since an appropriate vector taught by Stemmer is a plasmid such as pUC 18 (see column 12, lines 13-67) and it is known that a plasmid is a circular molecule, Stemmer discloses that said recombination of said first and second recombination sites insert into the vector and results in a circular molecule as recited in claim 17.

Regarding claims 19 and 20, since the oligonucleotides comprising one or more mutations taught by Stemmer can be single stranded and it is known that a single stranded

nucleic acid can be labeled with P^{32} at the 5' end in the presence of T4 polynucleotide kinase. According to the definition of "selectable markers" in the specification (see page 26, last paragraph bridging to page 27, first paragraph), selectable markers are DNA segments that bind products that modify a substrate, the oligonucleotides comprising one or more mutations taught by Stemmer are DNA segments that bind product that modify a substrate (ie., T4 polynucleotide kinase) or one or more selective markers as recited in claims 19 and 20.

Regarding claims 32 and 33, since Stemmer teaches that said first and second recombination sites are 5' and 3' ends of restriction sites (see above), Stemmer discloses that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33.

Regarding claim 44, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Stemmer teaches to digest a PCR product with restriction enzymes BamHI and Eco0109 and ligates digested PCR product into pUC18 digested with BamHI and Eco0109 (see column 12, lines 6-67). Since 3' and 5' of the digested PCR product taught by Stemmer has restriction sites, Stemmer discloses a first nucleic acid molecule comprising at least a first segment which comprises at least a first and a second recombination site (ie., 3' and 5'

restriction sites of the digested PCR product), wherein said segment comprises at least one integration sequence as recited in step (a) of claim 44. Since 5' and 3' ends of pUC18 contain restriction sites, Stemmer discloses a second nucleic acid molecule comprising at least a third and fourth recombination site (ie., 5' and 3' restriction sites of pUC18) as recited in steps (b) and (c) of claim 44. Since, during the ligation reaction, the digested PCR product must mix with pUC18 digested with BamHI and Eco0109 in the presence of a ligase, Stemmer discloses forming a mixture by mixing said first nucleic acid molecule (ie., the digested PCR product with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., pUC18 digested with BamHI and Eco0109) in the presence of at least one recombination protein (ie., a ligase) and incubating said mixture under conditions favoring recombination at least between said first (ie., the BamHI site on the digested PCR product) and third recombination sites (the BamHI site on the digested pUC18) and at least between said second (ie., the Eco0109 site on the digested PCR product) and fourth recombination sites (ie., the Eco0109 site on the digested pUC18), thereby transferring said first segment (ie., the digested PCR product) from said first nucleic acid molecule to said second nucleic molecule (ie., the digested pUC18) as recited in steps (b) and (c) of claim 44.

Regarding claims 45 and 46, since 3' and 5' of the digested PCR product taught by Stemmer has restriction sites (see above), Stemmer teaches that said first segment (ie., the digested PCR product) is flanked on one side by said first recombination site and is flanked on the other side by said second recombination site as recited in claim 45 wherein said first, second, third and fourth recombination sites are site-specific recombination sites as recited in claim 46.

Regarding claim 57, since the ligation reaction taught by Stemmer is performed in *in*

vitro (see column 12, lines 6-67), Stemmer discloses that said recombination (ie., the ligation taught by Stemmer) takes place *in vitro* as recited in claim 57.

Therefore, Stemmer teaches all limitations recited by claims 14-20, 27, 32, 33, 44-46, and 57.

Response to Arguments

In page 13, first paragraph bridging to page 16, second paragraph of applicant's remarks, applicant argued that: (1) "[*V*]*an Geuns* is distinguishable from the present case"; (2) "a recombination protein, as that term is defined and used in the present specification and claims, must have both endonuclease and ligase properties and exchange DNA segments. The Examiner, however, has selectively chosen phrases from the specification to fashion his own definition of 'recombination protein' as 'proteins that are involved in recombination reactions involving one or more recombination sites,' apparently ignoring part of the definition. See Office Action at page 4. Applicants respectfully submit that this is improper. Nevertheless, even using the Examiner's selective definition, 'recombination protein" must have endonuclease and ligase properties and exchange DNA segments because the recombination proteins 'are involved in recombination reactions involving one or more recombination sites.' Recombination sites are defined in the present specification as 'discrete sections or segments of nucleic acid on the participating nucleic acid molecules that are recognized and bound by a site-specific recombination protein during the initial stages of integration or recombination.' Specification at page 25, line 28 to page 26, line 3. In turn, the recombination proteins which recognize recombination sites *have endonuclease and ligase properties and exchange DNA segments.* See Specification at page 2, lines 3-9 and page 29, lines 12-22. Hence, a 'recombination protein' as that term is defined and used in the present

specification and claims, has both endonuclease and ligase properties, and exchanges DNA segments"; and (3) "the ligase taught by Stemmer does not have endonuclease activity".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the examiner agrees with applicant that "[*V*]*an Geuns* is distinguishable from the present case". However, *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993) is a case law that was used in Response to Arguments in previous office action but was not used for the rejection under 35 U.S.C. 102(b). This case law is commonly used by the office when applicant argues the limitation that is not cited in the claimed invention. Second, the definition in the specification at page 2, lines 3-9 and page 29, lines 12-22 suggested by applicant is definition for "site-specific recombinases" which is much narrower definition of "recombinant protein". However, there is no site-specific recombinase in the rejected claims. Third, the Examiner has not selectively chosen phrases from the specification to fashion his own definition of "recombinant protein" because, in the specification, "recombinant protein" is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). According to this definition for "recombinant protein", the ligase taught by Stemmer is a recombination protein.

4. Claims 14-20 , 27, 32, 33, 44-46, 56, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Atlung *et al.*, (Gene 107, 11-7, October 1991).

Atlung *et al.*, teach a versatile method for integration of modified genes and gene fusions into the bacteriophage lambda attachment site (attB) of the *Escherichia coli* chromosome.

Regarding claim 14, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Atlung *et al.*, teach to construct plasmid pTAC3599 by cloning a 740-bp Taq I fragment containing the promoter appYp into the Sama I site of pTAC3575 (see Figure 1 in page 12). Since the restriction sites of the 740-bp Taq I fragment containing the promoter appYp is recombination sites, Atlung *et al.*, disclose inserting one or more integration sequences comprising at least one recombination site (ie., the 740-bp Taq I fragment containing the promoter appYp) into at least one nucleic acid molecule (ie., pTAC3575) to produce one or more integration sequence-containing nucleic acid molecules as recited in claim 14. Since Atlung *et al.*, teach to ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 (see page 13, left column and Figure 2 in page 14) and it is known that a ligation reaction must be performed in the presence of a ligase, Atlung *et al.*, disclose transferring one or more integration sequence-containing nucleic acid molecules (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) comprising recombination sites (ie., restriction sites of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) into one or more vectors (ie., the

purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) in the presence of one or more recombination proteins (ie. the ligase) as recited in claim 14.

Regarding claims 16 and 18, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Atlung *et al.*, teach to construct plasmid pTAC3599 by cloning a 740-bp Taq I fragment containing the promoter appYp into the Sama I site of pTAC3575 (see Figure 1 in page 12). Since the restriction sites of the 740-bp Taq I fragment containing the promoter appYp is recombination sites, Atlung *et al.*, disclose inserting one or more integration sequences comprising at least one recombination site (ie., the 740-bp Taq I fragment containing the promoter appYp) into at least one nucleic acid molecule (ie., pTAC3575) as recited in claim 16. Since Atlung *et al.*, teach to ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 (see page 13, left column and Figure 2 in page 14) and it is known that a ligation reaction must be performed in the presence of a ligase, a nucleic acid molecule that is produced by inserting one or more integration sequences comprising at least one recombination site (ie., the 740-bp Taq I fragment containing the promoter appYp) into at least one nucleic acid molecule (ie., pTAC3575) and has the purified BstE II-Xho I fragment of

pTAC3599 carrying the phoA gene and the appYp-lacz fusion taught by Atlung *et al.*, comprises at least first (ie., BstE II site) and a second recombination sites (ie., Xho I site) as recited in claim 16 and Atlung *et al.*, disclose causing said at least first and second recombination sites (ie., BstE II and Xho I sites of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) to recombine in the presence of at least one recombination protein (ie., the ligase) as recited in claim 16. Since the restriction sites of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion taught by Atlung *et al.*, are located on 5' and 3' ends of the fragment, Atlung *et al.*, disclose that said first and second recombination sites are separated by a portion of said integration-sequence-containing nucleic acid molecule as recited in claim 18.

Regarding claims 15 and 27, since the purified BstE II-Xho I fragment of pTAC3599 carries the phoA gene and the appYp-lacz fusion, Atlung *et al.*, disclose that said nucleic acid molecule is genomic DNA as recited in claims 15 and 27.

Regarding claim 17, Since Atlung *et al.*, teach to ligate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion to the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 and generate a ligated circular molecule (see page 13, left column and Figure 2 in page 14), Atlung *et al.*, disclose that said recombination of said first and second recombination sites results in a circular molecule as recited in claim 17.

Regarding claims 19 and 20, since the integration sequences comprising at least one recombination site (ie., the 740-bp Taq I fragment containing the promoter appYp) taught by Atlung *et al.*, has an appYp (acid phosphatase transcriptional activator gene, see left column in

page 11), according to the definition of "selectable markers" in the specification (see page 26, last paragraph bridging to page 27, first paragraph), Atlung *et al.*, disclose that said integration sequence comprises one selectable marker (ie., appYp) as recited in claims 19 and 20.

Regarding claims 32 and 33, since Atlung *et al.*, teaches that said first and second recombination sites are 5' and 3' ends of restriction sites (ie., BstE II and Xho I sites) (see above), Atlung *et al.*, discloses that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33.

Regarding claims 44 and 56, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Since Atlung *et al.*, teach to generate the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion, Atlung *et al.*, disclose obtaining a first nucleic acid molecule comprising at least a first segment (ie., purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) which comprises at least a first and a second recombination site (ie., BstE II and Xho I sites) wherein said segment comprises at least one integration sequence as recited in step (a) of claim 44. Since Atlung *et al.*, teach the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463, Atlung *et al.*, disclose a second nucleic acid molecule comprising at least third and

fourth recombination sites (ie., BstEII and Sal I sites) as recited in step (b) of the claim. Since, during the ligation reaction, the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion must mixed with the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463 in the presence of a ligase, Atlung *et al.*, disclose forming a mixture by mixing said first nucleic acid molecule (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) in the presence of at least one recombination protein (ie., the ligase), and incubating said mixture under conditions favoring recombination at least between said first (ie., BstE II site from the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) and third recombination sites (ie., BstE II site from the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) and at least between said second (ie., Xho I site from the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) and fourth recombination sites (ie., Sal I site from the purified BstEII-Sal I fragment carrying the attP-aphA cassette from pTAC3463) thereby transferring said first segment (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) from said first nucleic acid molecule to said second nucleic molecule as recited in steps (b) and (c) of claim 44. Since Atlung *et al.*, teach to select colonies with the cassette integrated into the attB site of the E. Coli chromosome (see page 11, abstract), Hartley *et al.*, teach selecting for the second nucleic acid molecule

comprising said transferred first segment.

Regarding claims 45 and 46, since 3' and 5' of the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion taught by Atlung *et al.*, has restriction sites (see above), Atlung *et al.*, teaches that said first segment (ie., the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion) is flanked on one side by said first recombination site and is flanked on the other side by said second recombination site as recited in claim 45 wherein said recombination sites are site-specific recombination sites as recited in claim 46.

Regarding claim 57, since the ligation reaction taught by Atlung *et al.*, is performed in *in vitro* (see Table 1 in page 13 and Figure 2 in page 14), Atlung *et al.*, discloses that said recombination (ie., the ligation taught by Atlung *et al.*,) takes place in vitro as recited in claim 57.

Therefore, Atlung *et al.*, teach all limitations recited in claims 14-20, 27, 32, 33, 44-46, and 57.

Response to Arguments

In page 16, third paragraph bridging to page 20, third paragraph of applicant remarks, applicant argued that: (1) "the present specification defines an 'integration sequence' as 'any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule.' Specification at page 22, line 29 to page 23, line 2. In contrast, Atlung discloses the use of *traditional* cloning methods to ligate a nucleic acid segment that has been digested with restriction enzymes into a specific location in a plasmid that has *compatible ligation ends*. Thus, Atlung simply does not describe a nucleotide sequence capable of random insertion into a target nucleic acid molecule, and therefore does not describe integration sequences as that term is

described and used in the present specification and claims"; (2) "[A]tlung says absolutely nothing about microinjecting the BstE II-xho I fragment--or any other nucleic acid, for that matter--into a cell. Moreover, the mere fact that a DNA fragment microinjected into a cell can randomly insert into the cell's genome does not guarantee that it *will* happen. It is at least equally likely that when a DNA molecule is microinjected into a cell that it is not incorporated into the host cell genome, particularly if the host cell is a bacterium, where it is more likely that the microinjected DNA remains extra-genomic. Thus, the Examiner has not shown how the concept of microinjection of a DNA fragment is established from Atlung, nor that random insertion of DNA into a genome necessarily flows from the act of microinjecting DNA into a host cell. Thus, Atlung does not inherently teach the integration sequences as that term is defined and used in the present specification and claims"; and (3) in view of the specification at page 2, lines 3-9, and page 4, lines 15-20, "the ligation sites disclosed in Atlung are not recombination sites as that term is defined and used in the present specification and claims"

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion taught by Atlung *et al.*, is considered as an integration sequence in the rejection. Second, although Atlung *et al.*, do not teach microinjecting the BstE II-Xho I fragment into a cell, since the definition of "integration sequence" only requires that a nucleotide sequence is capable of inserting randomly into a target nucleic acid molecule (see the specification, page 22, last paragraph bridging to

page 23, first paragraph), it is known that a DNA can be randomly inserted in the genome of a cell if the DNA is microinjected into the cell, and applicant does not provide an evidence to show why purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion can not be inserted randomly into a target nucleic acid molecule, the purified BstE II-Xho I fragment of pTAC3599 carrying the phoA gene and the appYp-lacz fusion is capable of inserting randomly into a target nucleic acid molecule. Therefore, Atlung *et al.*, do teach integration sequences. Third, the definition in the specification at page 2, lines 3-9, and page 4, lines 15-20 suggested by applicant is definition for "site-specific recombinases" which is much narrower definition of "recombinant protein". However, there is no site-specific recombinase in the rejected claims. Fourth, since "recombination site" is defined as "a recognition sequence on a nucleic acid molecule participating in an integration/recombination reaction by recombination proteins" (see specification, page 23, last paragraph), ligation sites (restriction sites) can be considered as "recombination sites".

5. Claims 14-20, 27, 32-51, 56, and 57 are rejected under 35 U.S.C. 102(a) or 102 (e) as being anticipated by Hartley *et al.*, (US Patent No. 5,888,732, filed on June 7, 1996 and published on March 30, 1999).

Hartley *et al.*, teach recombinational cloning using engineered recombination sites.

Regarding claim 14, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph), "recombination site" is defined as "a recognition sequence on a nucleic acid molecule

participating in an integration/recombination reaction by recombination proteins" (see page 25, last paragraph), and "recombinant protein " is defined as "proteins that are involved in recombination reactions involving one or more recombination sites" (see the specification, page 25, second paragraph). Hartley *et al.*, teach a method of making chimeric DNA, which comprises: (a) combining *in vitro* or *in vivo* (i) an Insert Donor DNA molecule, comprising a desired DNA segment flanked by a first recombination site and a second recombination site, wherein the first and second recombination sites do not recombine with each other; (ii) a Vector Donor DNA molecule containing a third recombination site and a fourth recombination site, wherein the third and fourth recombination sites do not recombine with each other; and (iii) one or more site specific recombination proteins capable of recombining the first and third recombinational sites and/or the second and fourth recombinational sites; thereby allowing recombination to occur, so as to produce at least one Cointegrate DNA molecule, at least one desired Product DNA molecule which comprises said desired DNA segment, and optionally a Byproduct DNA molecule; and then, optionally, (b) selecting for the Product or Byproduct DNA molecule (see column 4, lines 47-67, column 5, line 1, and Figures 1, 2A, 3A, and 4A). Since Hartley *et al.*, teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site, Hartley *et al.*, disclose one or more integration sequences comprising at least one recombination site as recited in claim 14. Since Hartley *et al.*, teach to form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of an Insert Donor DNA molecule, a Vector Donor DNA molecule, and one or more site specific recombination proteins, Hartley *et al.*, disclose inserting one or more integration sequences comprising at least one recombination site (ie., an Insert

Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site) into at least one nucleic acid molecule (ie., the Vector Donor DNA molecule taught by Hartley *et al.*,) to produce one or more integration sequence-containing nucleic acid molecules as recited in claim 14. Since Hartley *et al.*, teach that, in the presence of a recombinase, the Cointegrate DNA molecule further forms least one desired Product DNA molecule which comprises said desired DNA segment with recombination sites (ie., attR and loxP in Figure 2A) and optionally a Byproduct DNA molecule (see Figures 1 and 2A), Hartley *et al.*, disclose transferring one or more integration sequence-containing nucleic acid molecules comprising recombination sites (ie., a nucleic acid from the Cointegrate DNA molecule with attR and loxP) into one or more vectors (ie., intprod in Figure 2) in the presence of one or more recombination proteins as recited in claim 14.

Regarding claim 16, since Hartley *et al.*, teach to insert an Insert Donor DNA molecule into a Vector Donor DNA molecule and form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of one or more site specific recombination proteins wherein the Insert Donor DNA molecule comprises a desired DNA segment flanked by a first recombination site and a second recombination site (see column 4, lines 46-67 and Figures 1, 2A, 3A, and 4A), Hartley *et al.*, disclose inserting one or more integration sequences (ie., the Insert Donor DNA molecule comprises a desired DNA segment flanked by a first recombination site and a second recombination site taught by Hartley *et al.*,), said one or more integration sequences comprising at least one recombination site, into at least one nucleic acid molecule (ie., Vector Donor DNA molecule taught by Hartley *et al.*,) thereby producing an integration sequence-containing nucleic acid molecule (ie., pEZC7cointegr in Figure 2) comprising at least a

first and a second recombination site (ie., attR and loxP); and causing said at least first and second recombination sites to recombine in the presence of at least one recombination protein (ie., Cre in Figure 2) as recited in claim 16.

Regarding claims 15 and 27, since Hartley *et al.*, teach that pEZC726 contains kanamycin resistance gene, Hartley *et al.*, disclose that said nucleic acid molecule is genomic DNA or cDNA as recited in claims 15 and 27.

Regarding claims 17 and 18, since Hartley *et al.*, teach the first and second recombination sites of pEZC705 (ie., attR and loxP) recombine with the third and fourth recombination sites of pEZC726 (ie., attP and loxP) to form pEZC7 cointegr (see Figure 2A), Hartley *et al.*, disclose that said recombination of said first and second recombination sites results in a circular molecule as recited in claim 17 wherein said first and second recombination sites (ie., att R and loxP) are separated by at least a portion of said integration sequence-containing nucleic acid as recited in claim 18 (see pEZC705 in Figure 2A).

Regarding claims 19 and 20, since the integration sequences (ie., the Insert Donor DNA molecule such as pEZC705) taught by Hartley *et al.*, has amp (an amplification resistance gene), according to the definition of "selectable markers" in the specification (see page 26, last paragraph bridging to page 27, first paragraph), Hartley *et al., et al.*, disclose that said integration sequence comprises one selectable marker (ie., amp) as recited in claims 19 and 20.

Regarding claims 32-39, since Hartley *et al.*, teach that the first and second recombination sites are attR and loxP respectively (see pEZC7cointegr in Figure 2A), Hartley *et al.*, disclose that said first and second recombination sites are site-specific recombination sites as recited in claims 32 and 33, said recombination sites are selected from the group consisting of

loxp, attB, attp, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism, or mutants or derivatives thereof as recited in claim 34, said recombination sites are selected from the group consisting of loxP, attB, attP, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism as recited in claim 35, at least one of said first and said second recombination sites is an att site or a mutant or derivative thereof as recited in claim 36, at least one of said first and said second recombination sites is an att site as recited in claim 37, said att site is selected from the group consisting of attB, attP, attL and attR, or a mutant or derivative thereof as recited in claim 38, said att site is selected from the group consisting of attB, attP, attL and attR as recited in claim 39.

Regarding claim 44, since Hartley *et al.*, teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site, Hartley *et al.*, disclose obtaining a first nucleic acid molecule (ie., the Insert Donor DNA) comprising at least a first segment which comprises at least a first and a second recombination site (ie., a desired DNA segment flanked by a first recombination site and a second recombination site) wherein said segment comprises at least one integration sequence as recited in step (a) of claim 44. Since Hartley *et al.*, teach to insert an Insert Donor DNA molecule into a Vector Donor DNA molecule and form at least one Cointegrate DNA molecule in at least one Cointegrate DNA molecule in the presence of one or more site specific recombination proteins capable of recombining the first and third recombinational sites and/or the second and

fourth recombinational sites wherein the Vector Donor DNA molecule containing a third recombination site and a fourth recombination site (see column 4, lines 46-67 and Figures 1, 2A, 3A, and 4A), Hartley *et al.*, disclose forming a mixture by mixing said first nucleic acid molecule (ie., the Insert Donor DNA molecule taught by Hartley *et al.*,) with at least one second nucleic acid molecule comprising at least a third and fourth recombination site (ie., the Vector Donor DNA molecule taught by Hartley *et al.*,) in the presence of at least one recombination protein, and incubating said mixture under conditions favoring recombination at least between said first and third recombination sites and at least between said second and fourth recombination sites, thereby transferring said first segment from said first nucleic acid molecule (ie., see nucleic acid segment from pEZC705 in PEZC7cointegr in Figure 2) from to said second nucleic molecule (ie., the Vector Donor DNA molecule taught by Hartley *et al.*,) as recited in claim 44.

Regarding claim 45, since Hartley *et al.*, teach that there is a nucleic acid segment between attB (ie., a first recombination site) and loxP (ie., a second recombination site), Hartley *et al.*, disclose said first segment is flanked on one side by said first recombination site and is flanked on the other side by said second recombination site as recited by claim 45.

Regarding claims 46-51, since Hartley *et al.*, teach that the first and second recombination sites are attB and loxP respectively (see pEZC705 in Figure 2A), Hartley *et al.*, disclose that said first and second recombination sites are site-specific recombination sites as recited in claim 46, said recombination sites are selected from the group consisting of loxP, attB, attP, attL, attR, FRT, a recombination site recognized by a resolvase, a bacterial transposable element, an integrating virus, an IS element, a P element of *Drosophila*, a bacterial virulence factor and a mobile genetic element for an eukaryotic organism as recited in claim 47, at least

one of said first and said second recombination sites is an att site or a mutant or derivative thereof as recited in claim 48, at least one of said recombination sites is an att site as recited in claim 49, said att site is selected from the group consisting of attB, attP, attL and attR, or a mutant or derivative thereof as recited in claim 50, said att site is selected from the group consisting of attB, attP, attL and attR as recited in claim 51.

Regarding claim 56, Hartley *et al.*, teach selecting for the second nucleic acid molecule comprising said transferred first segment (ie., the product DNA molecule) (see column 4, lines 46-65 and column 5, line 1).

Regarding claim 57, since the recombination reaction taught by Hartley *et al.*, is performed in vitro (see column 4, lines 46-67), Hartley *et al.*, disclose that said recombination takes place in vitro as recited in claim 57.

Therefore, Hartley *et al.*, teach all limitations recited in claims 14-20, 27, 32-39, 44-51, 56, and 57.

Response to Arguments

In page 20, last paragraph bridging to page 24, second paragraph of applicant's remarks, applicant argues that: (1) "[A]pplicants respectfully maintain that, for the reasons set forth in the previous Reply filed June 23, 2004, Hartley does not teach integration sequences as that term is defined and used in the present specification and claims. Specifically, as used in the present specification, '. . . an integration sequence is any nucleotide sequence that is *capable of inserting randomly* into a target nucleic acid molecule.' Specification at pages 22-23 (emphasis added). Thus, the Insert Donor DNA flanked by recombination sites as described in Hartley inserts into a nucleic acid molecule at specific recombination sites, and therefore does not insert randomly";

and (2) "[H]artley says absolutely nothing about microinjecting the Insert Donor DNA into a cell. Moreover, the mere fact that a DNA fragment microinjected into a cell can randomly insert into the cell's genome does not guarantee that it *will happen*. It is at least equally likely that when a DNA molecule is microinjected into a cell that it is not incorporated into the host cell genome, particularly if the host cell is a bacterium, where it is more likely that the microinjected DNA remains extra-genomic. Thus, the Examiner has not shown how the concept of microinjection of a DNA fragment is established from Hartley, nor that random insertion of DNA into a genome necessarily flows from the act of microinjecting DNA into a host cell. Thus, Hartley does not teach the integration sequences as that term is defined and used in the present specification and claims".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, according to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph). Since Hartley *et al.*, teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site, Hartley *et al.*, disclose one or more integration sequences comprising at least one recombination site (ie., an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site) as recited in the claims. Second, although Hartley does not teach microinjecting the Insert Donor DNA into a cell, since the definition of "integration sequence" only requires that a nucleotide sequence is capable of inserting randomly into a target nucleic acid molecule (see the specification, page 22, last paragraph bridging to

page 23, first paragraph), it is known that a DNA can be randomly inserted in the genome of a cell if the DNA is microinjected into the cell, and applicant does not provide an evidence to show why the Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site taught by Hartley *et al.*, can not be inserted randomly into a target nucleic acid molecule, the Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second recombination site taught by Hartley *et al.*, is capable of inserting randomly into a target nucleic acid molecule. Therefore, Hartley *et al.*, do teach integration sequences.

6. Claims 14-20, 27, 32-39, 44-51, 56, and 57 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The above patent (US Patent No. 5,888,732) was filed on June 7, 1996 and published on March 30, 1999 and taught all limitations recited in claims 14, 16-20, and 30-43 (see above). However, Gary Temple is not listed in above patent, he can not considered as inventor of this instant application. Please give explanation.

Response to Arguments

In page 24, third paragraph bridging to page 25, second paragraph of applicant's remarks, applicant argues that "[C]ontrary to the Examiner's assertions, the Inset Donor DNA Molecule disclosed in Hartley cannot be considered an integration sequence as that term is defined and used in the present specification. In any event, the invention claimed in Hartley is not identical to that claimed in present claims 14-20, 27, 32-39, 44-51, and 57. Accordingly, that Gary Templete

is not named as an inventor in Hartley is irrelevant to the propriety of his being name as an inventor in the present applicant".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because US Patent No. 5,888,732 does disclose the use of integration sequences (see above).

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 14-20, 27, 32-39, 44-51, and 57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-39 of U.S. Patent No.5,888,732. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but examined claims in this instant application are not

patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ormum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although independent claims 14-20, 27, 32-39, 44-51, and 57 in this instant application are not identical to claims 27-39 of U.S. Patent No.5,888,732, 27-39 of U.S. Patent No.5,888,732 are directed to the same subject matter and fall entirely within the scope of claims 14-20, 27, 32-39, 44-51, and 57 in this instant application. In other words, claims 14-20, 27, 32-39, 44-51, and 57 in this instant application are anticipated by claims 27-39 of U.S. Patent No. 5,888,732.

Response to Arguments

In page 24, third and fourth paragraphs of applicant's remarks, applicant argues that, "for the reasons discussed above distinguishing the presently claimed invention from the disclosure of Hartley, Applicants respectfully disagree with the Examiner's contention that the claims of the present invention are not patentably distinct from claims 27-39 of Hartley.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. According to the specification, "integration sequence" is defined as "any nucleotide sequence that is capable of inserting randomly into a target nucleic acid molecule" (see the specification, page 22, last paragraph bridging to page 23, first paragraph). Since claims 27-39 of U.S. Patent No. 5,888,732 teach an Insert Donor DNA molecule comprising a desired DNA segment flanked by a first recombination site and a second

recombination site, claims 27-39 of U.S. Patent No. 5,888,732 disclose one or more integration sequences comprising at least one recombination site as recited in claims 14 and 16.

Conclusion

9. This is a RCE of applicant's earlier Application No. 09/695,065. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

(1) The prior art that can be used for rejections under 35 U.S.C. 102(e) or 102(f) and double patenting:

Hartley et al., (U.S. Patent Nos. 6,171,861 B1, 6,270,969, and 6,277,608)

(2) The prior art that can be used for rejections under 35 U.S.C. 102(e) or 102(f):

Hartley et al., (U.S. Patent No. 6,143,557)

11. No claim is allowed.

162 Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
February 17, 2005

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600